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Review

Fatty acid elongases in mammals: Their regulation and roles in metabolism

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Abstract

A significant amount of the fatty acids synthesized by the cytosolic enzyme complex fatty acid synthase (FAS) or taken up by the diet are further elongated into very long chain fatty acids (VLCFA) in a four-step reaction cycle by membrane-bound enzymes predominantly located in the endoplasmic reticulum. Members of the *Elovl* (elongation-of-very-long-chain-fatty acids) gene family encode for enzymes (elongases), which are believed to perform the first, regulatory, step (condensation) in the elongation cycle in mammals. The family of enzymes consists of at least six members in mouse and human, believed to carry out substrate-specific elongation with fatty acids of different lengths and degrees of unsaturation.

The ability to synthesize VLCFA is a ubiquitous system found in different organs and cell types. However, VLCFAs seldom occur unesterified. Instead, they are joined either by an ester or amide linkage to a broad variety of different lipid species. VLCFA are most commonly found as building blocks in sphingolipids, although they are also important constituents of glycerophospholipids, triacylglycerols, sterol- and wax-esters.

To generalize, the fatty acid elongases can be divided into two major groups: (a) enzymes which are suggested to be involved in the elongation of saturated and monounsaturated VLCFA (ELOVL1, 3 and 6) and (b) enzymes which are elongases of polyunsaturated fatty acids (PUFA) (ELOVL2, 4 and 5). All the elongases exhibit specific spatial and temporal expression.

In this review, we will present and discuss the regulation of the mammalian fatty acid elongases and their potential role in lipid metabolism. We will consider both the biochemical functions of the proteins, as well as their role in a more physiological context.

Keywords Fatty acid elongation; Elongase; VLCFA; Lipid metabolism

Abbreviations: ACC, acetyl-CoA carboxylase; BAT, brown adipose tissue; CIG30, cold induced glycoprotein of 30 kDa; CNS, central nervous system; DGAT, diacylglycerol acyltransferase; DHA, docosahexaenoic acid; Elo, yeast elongase; ELOVL, elongation of very long chain fatty acids; EPA, eicosapentaenoic acid; FACE, fatty acid elongase; FAE, plant fatty acid elongase; FAS, fatty acid synthase; FIAF, fasting induced adipose factor; HEK, human embryonic kidney cells; HELO, human elongase; KAR, 3-ketoacyl-CoA reductase; LXR, liver X receptor; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; PEA, Caenorhabditis elegans elongase; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; rELO, rat elongase; SCD, steroyl-CoA desaturases; SREBP, sterol regulatory element binding protein; SSC, sequence similarity to cig30; TER, *trans*-2,3-enoyl-CoA reductase; VLCFA, very long chain fatty acids; WAT, white adipose tissue.

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Contents

1. Introduction

Much of our basic knowledge regarding fatty acid chain elongation in the endoplasmic reticulum (ER) derives from the pioneering work of Nugteren [72]. By using different rat liver cell fractions, he found that microsomes containing the ER fraction possessed the highest enzyme activity for elongating labeled fatty acyl-CoAs. This chain elongation process was clearly distinguished from de novo fatty acid synthesis found in the supernatant.

In mammals, fatty acids consisting of up to 16 carbons (palmitic acid) in length are synthesized by fatty acid synthase (FAS). Animal FAS functions as a homodimeric and multifunctional complex of ca 250 kDa found in the cytoplasm, which harbors seven different enzymatic activities in two catalytic centers. Synthesis of fatty acids by FAS is initiated by the elongation of a primer (i.e., acetyl or propionyl) with two-carbon units donated from malonyl-CoA and utilises NADPH as reductant in the elongation reaction. Repeating this reaction seven times in a cyclic manner enables FAS to ultimately produce the saturated C16 fatty acid, palmitic acid [20,87,103,104].

A significant amount of the fatty acids produced by FAS, as well as fatty acids taken up from the diet, are further elongated into long chain fatty acids containing 18 carbon atoms or longer, i.e., very long chain fatty acids (VLCFA). Formation of VLCFA is mainly performed in the ER by membrane-bound enzymes and the enzymatic steps involved in these processes are principally the same as described for FAS (Fig. 1). In contrast to the FAS complex, the four principal successive steps of VLCFA elongation are performed by individual proteins, which may be physically associated [19,51,72]. Three of the four enzymatic activities in VLCFA elongation are localized to the cytoplasmic side of ER membranes, while the enzyme performing the third step is suggested to be embedded in the membrane [74].

The reaction process begins with the condensation of an acyl-CoA molecule and malonyl-CoA, resulting in β-ketoacyl-CoA. The second step is a reduction reaction, which requires NADPH, where β-ketoacyl-CoA is converted to β-hydroxyacyl-CoA. β-Hydroxyacyl-CoA is subsequently dehydrated in the third step, resulting in enoyl-CoA which needs to be reduced by enoyl-reductase in the fourth step to complete the elongation cycle and generate an extended acyl-chain.

Further, the microsomes may utilize NADH, but under rate-limiting conditions a clear preference for NADPH was noticed [72]. The presence of fatty acid binding proteins, such as for example albumin, is necessary for optimal reaction [8,9].

Several attempts have been made to purify the enzymes involved in the microsomal elongation process, largely with an unsuccessful outcome owing to the hydrophobic properties of the proteins. In 1979, Bernert and Sprecher were able to solubilise and partially purify β-hydroxyacyl-CoA dehydrase from rat liver microsomes. The enzyme was free of condensation and enoyl-CoA reductase activity, which again shows that the chain elongation system consists of discrete enzymes in contrast to cytosolic FAS [7].